



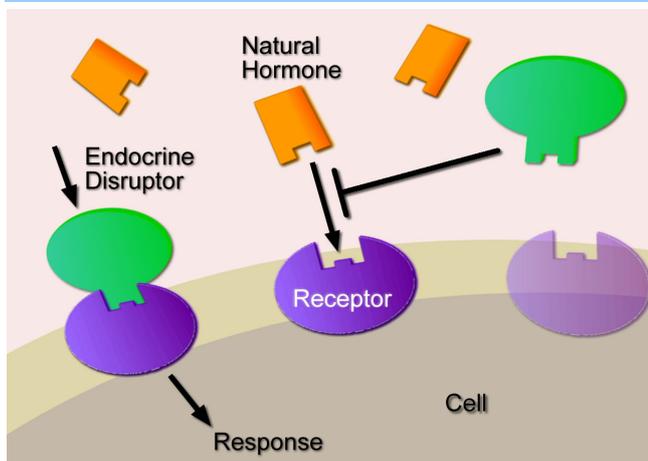
Health threats from endocrine disruptors A scientific and regulatory challenge

SUMMARY *Endocrine disruptors (ED) are substances that disturb the functioning of hormones and have negative effects on human health and wildlife. EDs can act at very low doses, and are especially dangerous during pregnancy and in infancy. Combinations of substances can have different effects to the same substances in isolation. Despite intense research efforts, there are still major gaps in understanding of endocrine disruption phenomena.*

The OECD coordinates the challenging task of defining internationally accepted test methods for EDs that can identify their adverse effects.

The registration and authorisation of EDs falls under the EU Chemicals Regulation (REACH). Other EU legislation restricts the use of EDs in toys, pesticides and biocides. The European Commission has started a review of the EU's Endocrine Disruptor Strategy, with the aim of establishing criteria for regulation. The EP's ENVI committee is working on an own-initiative report.

While the chemicals industry and some Member States propose to regulate only substances that are proven to cause adverse effects, NGOs advocate banning suspected EDs also. The Nordic countries have made a proposal to deal with the combination effects.



Endocrine disruptors mimic natural hormones.

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Issue definition

What are endocrine disruptors?

Endocrine disruptors are substances that cause adverse health effects by disturbing the production or activity of hormones in humans and animals.¹

Endocrine disruptors include dioxins, PCBs, phthalates,² parabens³ and bisphenol A. They can be found in plastics (baby bottles, food packaging...), food cans, furniture, cosmetics, shampoo, sunscreens, pharmaceuticals, pesticides, flame retardants and household dust. They can enter the body by breathing, eating, drinking or touching.

While research has demonstrated that many substances can influence the endocrine system,⁴ it is more challenging to identify which such influences actually have negative health impacts. More research and more data are needed to get a complete picture.

Effects on human health

Human endocrine-related disorders are becoming more frequent. EDs can cause reduced fertility and an increase in some diseases, including endometriosis and some cancers, and may play a role in obesity, diabetes, and cardiovascular diseases, immune functions and behavioural effects. Human health concerns about endocrine

disruptors include reproductive effects, such as sperm levels, reproductive abnormalities, and early puberty. Exposure of infants and foetuses to endocrine disruptors can affect the developing reproductive and nervous systems and organs.

A scientific revolution

The phenomenon of endocrine disruption was discovered only about 20 years ago. Since then, it has been studied extensively by thousands of researchers. Studies have shown that all parts of the endocrine system can be affected, and found a growing number of endocrine-active substances. Research has shown that these substances have some interesting properties:

- very low doses can have serious effects.
- a lower exposure may have a stronger effect than a higher exposure. The classic toxicological principle "the dose makes the poison" is not applicable, so that it is difficult to establish a safe threshold.
- EDs may have an effect only when an individual is exposed during a critical development window, for example at certain development stages as a foetus or during infancy. Exposure to EDs during critical development windows may cause a 'reprogramming' of the way genes are expressed during development.
- effects can occur long after the exposure, and long after the substance has disappeared from the body. For example exposure during infancy can lead to cancers in middle or old age.
- animal studies have shown epigenetic effects for up to seven generations of offspring.
- substances in mixtures may have different effects to the same substances in isolation (cocktail effect).

These properties make it hard to approach endocrine disruptors with established toxicological methods. As a result, there are still big gaps in the scientific knowledge, so risk assessment must be based on the best available evidence.⁵

In its [scientific statement](#), the Endocrine Society calls for a better link from basic research to clinical practice, better information of healthcare personnel, and for better regulation of EDs

Effects on wildlife

Endocrine disruption has been observed on a number of wild species.⁶ The observed effects include feminisation, reproductive failure, immune dysfunction, hermaphroditism, and egg-shell-thinning. Striking examples are male frogs with female organs, and male fish which produce eggs. Pesticides and sewage contribute to the presence of EDs in natural ecosystems.

There are still considerable gaps in the identification of substances that affect wildlife, and no cost-effective testing methods exist at the moment.

EU policy

Community strategy

In 1999 the Commission adopted the '[Community strategy for endocrine disruptors](#)' (COM(1999) 706), following stakeholder consultation. The strategy includes the establishment of a list of priority substances, harmonisation of new testing methods, research and information exchange, and updating of legislation.

[The fourth implementation report of the Community Strategy for Endocrine Disruptors](#) (SEC(2011) 1001) was published in August 2011. It notes that a [priority list](#) has been established. Research on endocrine disruptors is carried out at the Commission's Joint Research Centre and in [projects](#) supported through the research framework programmes. Considerable efforts have been made to develop criteria and tests for identifying EDs. In February 2011, the Commission [added three EDs](#) to the list of substances which are subject to authorisation under REACH.

The [state-of-the-art assessment of endocrine disruptors](#), produced for the European Commission, was published in February

2012. It outlines the properties of endocrine disruptors, including their potential to cause irreversible and delayed effects, which justify placing them in a separate regulatory category. The report discusses test methods for EDs and proposes a new approach.

The European Commission has launched a [review of the ED strategy](#) which it plans to complete by November 2012. A [conference](#) with experts and stakeholders took place in June 2012.

In December 2009, the Council adopted [conclusions on combination effects of chemicals](#), asking the Commission to make recommendations on how to address exposure to multiple endocrine disruptors. In response, an [EU scientific opinion](#) was published in February 2012. However, it has been [criticised for failing to fully address the risk](#) from chemical mixtures with different modes of action.

The [Presidency Conclusions](#) of an informal meeting of Ministers for Environment in April 2012 call for a “beyond REACH strategy for a toxic-free environment addressing combination effects of chemicals and safety concerns related to endocrine disruptors”.

The [Council Conclusions of 11 June 2012](#) call for initiatives regarding EDs. under the Seventh Environment Action Programme.

EU legislation

The regulation of chemical substances falls under the [REACH \(Registration, Evaluation, Authorisation and Restriction of Chemicals\) Regulation](#) ((EC) 1907/2006). Article 57f of REACH provides for the regulation of EDs as substances of ‘equivalent concern’ on a case by case basis. The Commission must review the REACH Regulation's approach to endocrine disruptors by June 2013.

The REACH Regulation requires an evaluation of chemical substances which are considered as potentially dangerous. The first [Community Rolling Action Plan](#) for the evaluation of chemicals contains 90 substances, including many suspected EDs.

Bisphenol A (BPA)

BPA is widely used, for example in plastics, CDs, food packaging, toys, cash receipts, and water pipes. Around 4 million tonnes are produced worldwide each year. A [German study](#) found BPA (in low concentrations) in the urine of 99% of children.

BPA acts like oestrogen at very low doses to enlarge the prostates and lower sperm counts. It is suspected of causing breast cancer, obesity and diabetes. There is, however, no consensus on the health risks posed by BPA in everyday life.

Denmark was the first EU country to [ban BPA](#) in baby bottles and in the packaging of food for children under the age of three (from July 2010). [European Commission Directive 2011/8/EU](#) prohibits the production (since March 2011) and sale (since June 2011) of baby bottles containing BPA. The Swedish government has gone further and [decided](#) on 13 April 2012 to ban BPA in the packaging of food for children under the age of three and to assess the use of BPA in receipts and tickets, drinking water pipes and toys. [Belgium decided](#) on a ban on BPA in all food contact materials aimed at children under three years old, which will come into effect on 1 January 2013. A [proposed French law](#) to ban BPA from all food containers from 2014 onwards has been [opposed by several EU Member States](#) because it would distort the internal market.

On the other hand, in 2010 the European Food Safety Authority (EFSA) [reconfirmed a tolerable daily intake](#) of 0.05 mg per kg of body weight which was set in 2006. The agency found that daily intakes through food and drink are well below this level. In order to take the latest research on low-dose effects into account, EFSA has just launched a re-evaluation. The US Food and Drugs Administration also [considers BPA as safe](#).

However, the information and testing requirements in the EU chemicals legislation comprise only part of the endocrine-disrupting effects that can be measured

with internationally agreed and validated test methods.

[Regulation \(EC\) 1272/2008 on classification, labelling and packaging of substances and mixtures](#) implements the [Globally Harmonised System \(GHS\)](#) for classification and labelling of chemicals. It does not have a specific class for endocrine disruptors, which may however be treated as substances of 'equivalent concern'.

The [Plant Protection Product Regulation](#), (EC 1107/2009) and the new [Biocides Regulation](#) prohibit products with endocrine-disrupting properties. Both regulations require the Commission to specify scientific criteria for the determination of endocrine-disrupting properties by 13 December 2013.

The [Water Framework Directive](#) (2000/60/EC) allows for the treatment of EDs as substances of 'equivalent concern', analogous to REACH. The Commission has [proposed to add two EDs to the list of priority substances](#) in the field of water quality (ordinary legislative procedure).

The new [Toy Safety Directive](#) (2009/48/EC) gives the Commission the possibility to set limit values for substances, including EDs.

[Regulation \(EC\) 1223/2009 on cosmetic products](#) does not yet include any provisions concerning EDs, but foresees a review of the Regulation as soon as internationally agreed criteria are available, or at the latest by January 2015.

Current EU legislation offers only limited possibilities for assessing the cumulative effects of different substances on the endocrine system.

Role of the European Parliament

On 20 October 1998, the EP adopted a resolution on the classification of EDs. On 26 October 2000, it adopted a [resolution on endocrine disruptors](#) calling on the Commission to identify substances for

immediate action, and provide support for research and international cooperation.

On 20 April 2012, the EP adopted a [resolution on the Seventh Environmental Action Programme](#) calling for specific measures relating to emerging threats, including endocrine disruptors and combination effects of chemicals.

On 4 October 2011, the ENVI Committee discussed oral question No 2011/07 "on endocrine disruptors and cocktail effects" by Linda McAvan and Christel Schaldemose with Commission staff. The ENVI Committee has started a procedure for an INI Report "The protection of public health from endocrine disruptors" (ENVI/7/08967, rapporteur Åsa Westlund, S&D).

International organisations

In 2002, UNEP/WHO published a [review on endocrine-disrupting effects](#), which is currently being updated.

International cooperation on EDs has been [nominated as an emerging policy issue](#) for the [third International Conference on Chemicals Management](#) in September 2012.

In 1996, the OECD set up a task-force for [endocrine disruptors testing and assessment](#), which develops and validates internationally accepted test methods.⁷ The [OECD environmental outlook 2050](#) highlights the need for better testing and assessment methods for EDs.

Issues at stake

In order to identify and regulate EDs, a number of decisions must be taken:

- How should the precautionary principle be applied? Should an endocrine-active substance be regulated if it is suspected of causing adverse effects, but there is no scientific proof?
- Should regulation be based on "hazard assessment" (possibility of adverse effects) or on "risk assessment" (likelihood of adverse effects)?

- Should independent peer-reviewed studies be taken into account, or only studies conforming to the OECD's Good Laboratory Practice⁸ standard?
- Can results of in-vitro tests on cell tissues be accepted, or only results from in-vivo tests on living organisms?
- How is exposure to multiple substances to be treated, given that it is not possible to test all combinations of substances?
- What role should potency (measure of strength of an active chemical substance) play in ED regulation?
- Do harmless substances exist which can substitute for a wide range of ED uses?

The [State-of-the-art Assessment Report](#) requested by the European Commission notes that internationally agreed testing methods do not capture the full range of endocrine effects, and argues for identifying EDs using a weight-of-evidence approach. The report argues for the creation of a separate regulatory category for EDs.

A [report for the European Environment Agency](#) argues for a regulatory framework that deals pragmatically with incomplete scientific knowledge.

Stakeholder views

EU Member States

Germany and the UK have published a [position paper](#), proposing potency-based cut-off criteria to define endocrine disruptors for regulatory purposes.⁹

The [Swedish and French governments](#) highlight an urgent need for comprehensive risk management measures in order to ensure that products consumed by children are safe beyond any doubt.

Denmark submitted a proposal for [criteria for ED and options for regulation](#) in 2011. The proposal foresees classification of: ED (no approval unless negligible exposure), suspected ED (approval requires further data) and indicated ED. The proposal recommends that applicants under REACH be obliged to assess endocrine-disrupting

properties of substances, that substances be screened for endocrine-disrupting properties, and that potential EDs undergo substance evaluation.

The [Nordic Council of Ministers](#) proposed that chemical combination effects should be approached horizontally in the EU, and that only a part of the "safe dose" should be allowed in each area of regulation.

Industry

The [European Chemical Industry Council](#) (CEFIC) supports an approach which links endocrine mechanism to an adverse health effect, and a risk-management approach which includes an assessment of exposure.

NGOs

Various NGOs¹⁰ have published a [common position on ED regulation](#) calling for a testing strategy that addresses the complexity of the endocrine system, considers non-GPL certified studies, and minimises testing on animals. They advocate the use of REACH to speed up regulation of EDs, and the exclusion of EDs from authorisation under the 'adequate control' route of REACH. They propose a precautionary approach which errs on the side of caution in case of scientific uncertainty.

The environmental NGO ChemSec has established [SIN List 2.0](#), a list of priority substances, including EDs, that should be evaluated under REACH. European trade unions have drawn up a complementary [Trade Union Priority List](#) of substances.

ChemSec and other environmental and health NGOs welcomed the State-of-the-art Assessment Report and called on the Commission to follow its recommendations. BEUC, the European consumers' organisation, supports a separate regulatory category for EDs.

WECF, [Women in Europe for a Common Future](#), says the Toy Safety Directive does not go far enough in banning EDs and in mandatory testing of toys for safety.

Main references

[Global assessment of the state-of-the-science of endocrine disruptors](#) / WHO, 2002

[State of the Art Report on Mixture Toxicity](#) / Andreas Kortenkamp et al., December 2009

[State of the art assessment of endocrine disrupters: final report](#) / Andreas Kortenkamp et al., December 2011

[Endocrine-disrupting chemicals: an Endocrine Society scientific statement](#) / E. Diamanti-Kandarakis et al., *Endocrine Reviews* 30(4):293-342, 2009.

[The impacts of endocrine disrupters on wildlife, people and their environments – The Weybridge+15 \(1996–2011\) report](#) / European Environment Agency, 10 May 2012.

[Fourth implementation report of the Community Strategy for Endocrine Disruptors](#) / European Commission, 2011

[Endocrine Disruptors Website \(DG ENVI\)](#)

[Effects of pollutants on the reproductive health of male vertebrate wildlife - males under threat](#) / Gwynne Lyons, CHEM Trust, 2008

[Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses](#) / Laura N. Vandenberg et al., *Endocrine Reviews* 33:3, p. 378-455, June 2012

[The Endocrine Disruption Exchange \(TEDX\)](#)

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Endnotes

- ¹ The endocrine system consists of glands, such as the thyroid, gonads and adrenal glands, which produce hormones such as adrenaline, oestrogen and testosterone. Hormones are signalling molecules, which guide the development, growth, reproduction and behaviour of humans and animals. EDs can disturb the endocrine system in different ways: They can mimic natural hormones and bind to receptors, giving a signal that is too strong or occurs at the wrong time. They can bind to a receptor and prevent the correct hormone from binding, preventing the body from responding properly. They can block the way natural hormones and receptors are made or controlled.
- ² Millions of tonnes of phthalates are used every year as softeners in plastics, solvents and fragrance carriers. The group of "low phthalates" can have oestrogenic effects and cause deformities of male reproductive organs, premature breast development and breast cancer.
- ³ Parabens are used as preservatives in cosmetics and personal care products. They can have oestrogenic (feminising) and anti-androgenic (inhibiting male characteristics) effects.
- ⁴ Substances that influence the endocrine system but do not necessarily cause adverse health effects are called 'endocrine modulators' or 'endocrine active substances'. Endocrine active substances such as phytoestrogens can also occur naturally in food, such as carrots and soybeans.
- ⁵ [A Clash of Old and New Scientific Concepts in Toxicity, with Important Implications for Public Health](#) / John Peterson Myers, R. Thomas Zoeller, and Frederick S. vom Saal, *Environmental Health Perspectives* 117(11), 2009.
- ⁶ ED effects have been studied for example in marine snails, frogs, birds, fish, seals, alligators, and polar bears. Despite the progress which has been made in understanding endocrine disruption in wildlife, very little is known about the endocrinology of most mammals (only two per cent have been described), and even less about amphibians, invertebrates, reptiles and birds.
- ⁷ With mutual acceptance of test data, the amount of testing can be reduced and the costs can be shared.
- ⁸ The [Good Laboratory Practice](#) (GLP) standard aims at high quality test data and is a precondition for mutual acceptance of data. Many regulatory agencies do not take into account studies which do not follow the GPL standard.
- ⁹ The State-of-the-art Assessment Report argues that such potency-based cut-off criteria are "not scientifically justifiable" because the values are "largely arbitrary". Instead, potency should be considered alongside other properties including irreversibility and severity of effects.
- ¹⁰ CHEM Trust, European Environmental Bureau, Pesticide Action Network Europe, Health and Environment Alliance, ClientEarth, Global 2000, BUND, ISTAS/CCOO, Cancer Prevention & Education Society, ChemSec, Women in Europe for a Common Future.